Br. J. clin. Pharmac. (1987), **23**, 99–101

Nefopam excretion in human milk

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Human milk and plasma samples were obtained from five healthy nursing mothers who were taking nefopam hydrochloride (60 mg four-hourly) for post-episiotomy pain. Concentrations of nefopam were quantified in milk and plasma paired samples, taken daily from birth for 5 days, by a specific paired-ion reverse phase h.p.l.c. method. Although nefopam was present in human milk in an equivalent concentration to plasma (milk:plasma ratio 1.2 ± 0.7, mean ± s.d.), the likely infant exposure was less than 0.05 mg kg^{-1} day^{-1} which, on a body weight basis, would be less than 3% of the maternal dose.

Keywords nefopam human milk analgesic

Introduction

Nefopam hydrochloride (Acupan®) is an established analgesic drug unrelated chemically and pharmacologically to other analgesics. It is effective orally and intramuscularly for the treatment of a wide range of painful conditions (for review see Heel *et al.*, 1980). In particular, Bloomfield *et al.* (1980) have shown that nefopam relieves the pain associated with episiotomy. Recognising that the breast-fed newborn infant may be the unintended recipient of drugs administered to the mother, a study was designed to investigate the excretion of nefopam in breast milk.

Most drugs are likely to be excreted into breast milk to some extent and consumed by a suckling infant. Although there are no data on the excretion of nefopam into human milk, this would be expected to occur to some extent since nefopam is a relatively small molecule (m.wt 289.8), it is a base (pKa 9.36) which is only approximately 70% protein bound in plasma and the pH of milk is generally slightly lower than that of plasma.

Methods

Protocol

The study protocol was approved by the Hospital Ethics Committee and each subject gave informed verbal and notated consent before inclusion in the study. Five healthy nursing mothers ranging in age from 20 to 27 years (mean 22.5 years) and weighing post delivery between 56.8 and 91.1 kg (mean 75.5 kg) took part. All subjects were studied during the hospital stay after giving birth.

Nefopam hydrochloride (2 × 30 mg Acupan®) was prescribed for post-episiotomy pain relief every 4 h. The regimen was followed for 48 h when most mothers found there was less need for pain relieving therapy. However, two subjects had additonal doses. Subject 3 had 60 mg at 76 h and 84 h and Subject 4 had 60 mg at 61.5 h and 85.5 h after the first dose.

Approximately 10 ml blood samples were drawn from an ante-cubital vein into heparinised tubes daily for 5 consecutive days. After centri-

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fugation the plasma was stored at −20° C until analysis. Milk (5–10 ml) was collected by breast pump or manual expression at approximately the same time as the venepuncture and also stored at −20° C. Blood pressure, pulse, temperature and respiration for all subjects were monitored as per ward routine. Co-proxamol was available as additional analgesic therapy if required.

Analytical

Nefopam (base) concentrations in milk and plasma were determined at Simbec Research Ltd, Merthyr Tydfil by a new paired-ion reverse phase h.p.l.c. method. Briefly, 2 ml of biological fluid was pipetted into an extraction tube and spiked with 100 μl of 0.1 mg/100 ml *N*-isopropyl-*N*-desmethyl nefopam internal standard solution. The samples were alkalinised by the addition of 200 μl of 1M glycine buffer (pH 11.0) and then extracted by mechanical shaking with cyclohexane (6 ml). After centrifugation, the upper organic phase was transferred to a second extraction tube containing 0.1 M HCl (3 ml). The tube was shaken and centrifuged as before and the organic layer discarded. The samples were alkalinised with 0.5 M NaOH (1 ml) and extracted in cyclohexane (6 ml). After centrifugation the organic phase was transferred to a silanised vial and evaporated to dryness under a stream of nitrogen. The residue was dissolved in 70 μl of h.p.l.c. mobile phase for injection onto the h.p.l.c. column. The mobile phase was acetonitrile:0.01 M sodium pentane sulphonic acid (pH 3.15) in the proportions 50:55 and it was pumped at 1.5 ml min^{-1} through a 25 cm × 4.6 mm i.d. Zorbax CN 7 μm column (Dupont Instruments, England). The column effluent was monitored by ultraviolet detector set at 215 nm. The minimum

Table 1 Human milk and plasma concentrations of nefopam in nursing mothers during oral dosing over 4 days with 60 mg nefopam hydrochloride given 4 hourly (a total of 12 doses). First dose was given at time 0 h

	Time (h)		*Nefopam concentration (ng ml^{-1})*		*Concentration ratio*
Subject	*Plasma*	*Milk*	*Plasma*	*Milk*	*Milk:Plasma*
1	6.0	6.3	26.0	28.5	1.1
2	5.0	5.0	34.2	110.3	3.2
3	4.7	5.0	44.7	76.4	1.7
4	5.5	5.5	31.2	68.1	2.2
5	5.0	4.8	6.3	IS	—
1	30.7	30.5	186.0	97.7	0.5
2	28.7	28.8	105.8	110.9	1.0
3	28.7	28.8	168.4	124.9	0.7
4	29.6	29.5	150.0	182.0	1.2
5	29.0	28.5	80.3	193.8	2.4
1	50.5	50.0	83.5	77.3	0.9
2	47.3	46.0	259.6	298.7	1.2
3	48.0	52.8	233.4	89.0	0.4
4	49.7	49.5	238.0	202.5	0.9
5	48.0	51.0	291.4	89.0	0.3
1	74.0	74.0	3.0	5.8	1.9
2	74.2	74.3	28.4	28.4	1.0
3	72.0	71.7	29.3	28.5	1.0
4**	77.5	73.5	73.9	36.6	0.5
5	76.7	78.0	5.2	8.3	1.6
1	98.5	98.0	ND	ND	—
2	NS	NS	—	—	—
3*	101.0	101.0	22.9	16.7	0.7
4**	97.7	97.5	25.4	26.9	1.1
5	101.0	101.0	ND	ND	—

NS = no sample; ND = not detected; IS = insufficient sample
* Additional 60 mg nefopam doses at 76 and 84 h
** Additional 60 mg nefopam doses at 61.5 and 85.5 h

detectable nefopam level with 80% confidence limits was 1.6 ng ml^{-1}.

Results

The levels of nefopam in human milk and plasma during oral dosing for 4 days with 60 mg nefopam hydrochloride given 4 hourly are presented in Table 1.

Subject 2 required additional analgesic therapy throughout the study. No adverse events were reported.

Once dosing ceased, nefopam levels in plasma and milk samples decreased in parallel. Nefopam was not detected in the final plasma or milk samples taken on day 5 from the two subjects who had not received additional nefopam doses.

Discussion

The aim of this study was to assess the dose of nefopam received by the suckling infant of a mother being treated with the analgesic nefopam, for pain associated with episiotomy. As blood is usually taken for haemoglobin estimation on the third day post-partum, only four additional venepunctures were required thus minimising discomfort to the mother.

Paired plasma and milk samples were taken between 1 and 3 h after the second, eighth and twelfth doses when maximum maternal plasma concentrations would be expected (Heel *et al.*, 1980) and in three subjects, twice after dosing had been stopped.

Nefopam was present in human milk in similar concentrations to that in plasma (milk:plasma ratio 1.2 ± 0.7 mean ± s.d.). Assuming a milk intake by a 3 kg neonate of 600 ml day^{-1} (Wilson *et al.*, 1980) and using the highest concentration measured in the study, the maximum daily dose of nefopam received by the baby would be approximately 0.05 mg kg^{-1} day^{-1}. For adults, the minimum recommended dose of nefopam is 1.5 mg kg^{-1} day^{-1}, therefore, on a body weight basis, the infant dose would be less than 3% of the maternal dose.

The authors are grateful to A. J. Woodward, P. R. Robinson, P. Davies, P. A. Lewis and A. Franks at Simbec Research Ltd.

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(Received 20 March 1986, accepted 20 September 1986)